FREEDOM OF INFORMATION SUMMARY

NADA 141-203

DERAMAXX™ Chewable Tablets
(deracoxib)

" for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs."

Sponsored by: Novartis Animal Health US, Inc.
3200 Northline Avenue Suite 300
Greensboro, NC 27408

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FREEDOM OF INFORMATION SUMMARY

I. General Information

A. File Number: 141-203

B. Sponsor: Novartis Animal Health US, Inc
3200 Northline Avenue Suite 300
Greensboro, North Carolina 2740

C. Established Name: deracoxib

D. Proprietary Name: DERAMAXX™ Chewable Tablets

E. Dosage Form: scored, flavored tablets

F. How Supplied: The product is available as 25 mg and 100 mg round, brownish, half-scored tablets in 7, 30, and 90 count bottles.

G. How Dispensed: Prescription (Rx) – US Federal law restricts this drug to use by, or on the order of, a licensed veterinarian.

H. Amount of active ingredient: Each tablet contains 25 mg or 100 mg of deracoxib.

I. Route of Administration: oral

J. Species/Class: dogs

K. Recommended Dosage: The recommended daily dose of DERAMAXX tablets for postoperative orthopedic pain is 3-4 mg/kg/day (1.4 to 1.8 mg/lb/day) as a single daily dose, as needed for 7 days. Tablets are scored and dosage should be calculated in half-tablet increments.

L. Pharmacological Category: Non-steroidal anti-inflammatory drug (NSAID)

M. Indications: DERAMAXX™ Chewable Tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs $\geq$ 4 lbs (1.8 kg).

II. Effectiveness

A. DOSAGE CHARACTERIZATION:

A once daily, oral dose of 3-4 mg/kg of deracoxib was based on the results of a study to evaluate the drug's effectiveness in a surgical model of cranial cruciate ligament repair in dogs. Dogs received deracoxib or a placebo 30 minutes before surgery and once daily for 14 days. Dogs were assigned to a 0, 2, 4, or 6 mg/kg/day group. Pain and lameness assessments were evaluated for each dog in the 4 groups. These evaluations included a clinical assessment of pain and lameness, a measurement of the range of motion in the surgical stifle, and forceplate evaluation.

A subjective and objective baseline evaluation of pain and lameness was made prior to drug administration and at 13 assessment times postoperatively. Pain and lameness scores were statistically significant from the 18th hour post-surgery (assessment #3) through the 24th hour of Day 7 (assessment #9) following administration. Many dogs across all treatment groups were partially or non-weight bearing postoperatively on the affected limb, limiting the collection of sufficient forceplate data.

The average clinical pain and lameness scores for the 4 mg/kg deracoxib group showed statistically significant improvement ($p< 0.05$) within the first day post-surgery (similar improvement was noted in the 2 mg/kg deracoxib group within three days post-surgery). These results support the effectiveness of deracoxib at 4 mg/kg for the control of orthopedic postoperative pain and inflammation.

One dog in the 6 mg/kg/day group was considered a surgical failure (lack of joint stability). The impact of postoperative activity on this dog is unknown. The percentage of pre- to post-study urine samples with detectable levels of bilirubin decreased for all dose groups, with the exception of the 6 mg/kg dose group. The percentage of urine samples in this group with detectable levels of bilirubin increased from 0 to 20%. Pre-surgical cytologic synovial fluid analysis of all dogs showed no evidence of inflammation. Post-surgical cytological analysis revealed varying degrees of neutrophilic inflammation (mild to suppurative) in deracoxib-treated dogs. One synovial sample in the 4 mg/kg deracoxib group cultured positive for *S. aureus*, and one sample in the 6 mg/kg group was suggestive of sepsis, although no culture was done.

Summary Conclusion: Clinicopathologic abnormalities were identified at 6 mg/kg. Based on evaluation of the clinical pain and lameness scores, the effective deracoxib dose selected for the control of postoperative orthopedic pain and inflammation is 3-4 mg/kg/day, when given 30 minutes before surgery.

B. SUBSTANTIAL EVIDENCE:

1. Field Study

The effectiveness of DERAMAXX™ Chewable Tablets for the control of postoperative orthopedic pain and inflammation was evaluated in dogs presented for surgical repair of a cranial cruciate ligament injury. The study was conducted at six veterinary clinics throughout the U.S. Results of the study demonstrate that DERAMAXX™ Chewable Tablets are safe and effective when administered at a dose of 3-4 mg/kg of body weight once daily for a maximum of 7 days.

The intensity of surgical pain varied with the duration of the procedure and individual response to pain; therefore, the requirement for pain control may have varied amongst cases.

A variety of drugs was used in conjunction with the surgical procedure. Surgical inductions included the use of combinations of pre-anesthesia medications, barbiturates, inhalant anesthetics, anticholinergics, antibiotics and parenteral fluids.

a. Type of Study: Placebo-Controlled, Masked, Randomized Field Study

b. Investigators:

Michael G. Conzemius, DVM, Dipl. ACVS Veterinary Teaching Hospital Iowa State University Ames, IA 50011-1250	Katherine L. Wells, DVM Metroplex Veterinary Centre 700 Airport Freeway West Irving, TX 75062
Brian S. Beale, DVM, Dipl. ACVS Gulf Coast Veterinary Specialists 1111 West Loop South, Suite 160 Houston, TX 77027	David C. Sweet, VMD, Dipl. ACVS Jill L. Sammarco, BVSc, MRCVS, Dipl ACVS, Dipl. ECVS Veterinary Referral Centre 48 Notch Road Little Falls, NJ 07424
Darryl L. Millis, DVM, Dipl. ACVS College of Veterinary Medicine University of Tennessee Knoxville, TN 37996-4500	Alan J. Lipowitz, DVM, Dipl. ACVS College of Veterinary Medicine University of Minnesota St. Paul, MN 55108

c. General Design:

i) Purpose: The study objective was to evaluate the clinical effectiveness and safety of DERAMAXX tablets at a dose of 3-4 mg/kg orally once daily for 7 days, for the control of postoperative orthopedic pain associated with cranial cruciate ligament repair. The protocol allowed

for a single dose of butorphanol for control of pain, if additional analgesia was warranted in the opinion of the investigator.

ii) Test animals: Two hundred and seven client-owned male and female dogs ranging from 1-15 years of age, representing 43 different breeds were included in the study. A total of 59 dogs treated with deracoxib and 60 dogs that received a placebo were evaluated for effectiveness. One hundred and five dogs treated with deracoxib and 102 dogs that received a placebo were included in the safety evaluation.

iii) Control: The placebo was identical to DERAMAXX tablets without the active ingredient.

iv) Dosage form: DERAMAXX tablets (final market formulation)

v) Route of administration: Oral

vi) Dosage used: 3-4 mg/kg (1.4- 1.8 mg/lb) administered the evening before surgery, then once daily for 6 days postoperatively.

vii) Test duration: 7 days

viii) Parameters measured: Seven days pre-study, and on Days 2, 3, 4, and 7, the investigators assessed each dog for lameness at a walk, lameness at a trot, and pain on palpation of the affected stifle, joint mobility, as well as the need for additional postoperative analgesia.

Prior to the study and again on Day 7, hematology and clinical chemistry samples were obtained.

d. Results: One hundred and nineteen (119) dogs were included in the overall effectiveness analysis. Statistically significant differences ($p< 0.05$) favored deracoxib at all postoperative evaluations for lameness at a walk, lameness at a trot, and pain on palpation scores. See Table 1.

Table 1. Deracoxib vs. Placebo

	P-values of the statistical comparison of deracoxib vs. placebo		
Time (hrs)	Lameness at Walk	Lameness at Trot	Pain on Palpation
0	0.828	0.966	0.351
24	<0.001	0.003	0.004
48	<0.001	<0.001	<0.001
72	<0.001	<0.001	<0.001
144	<0.001	<0.001	0.026

One DERAMAXX tablet-treated dog was treated with medetomidine for dysphoria during anesthetic recovery. The reversal agent, atipamezole, was then administered, and the dog recovered uneventfully. Twenty-two placebo and 14 DERAMAXX tablet-treated dogs received postoperative butorphanol injections. Two placebo-treated dogs and 1 DERAMAXX tablet-treated dog required additional analgesia in excess of the single butorphanol injection (treatment failures).

Four DERAMAXX tablet- and 5 placebo-treated dogs were withdrawn from the study due to adverse events including vomiting, diarrhea, and insufficient analgesia. There were no statistically significant changes in the mean values for hepatic or renal clinical pathology indices between DERAMAXX tablet- and placebo-treated dogs. Four DERAMAXX tablet- and 2 placebo-treated dogs with normal pretreatment values exhibited elevated postoperative serum bilirubin values. Three DERAMAXX tablet- and one placebo-treated dog with normal pretreatment values exhibited elevated postoperative ALT (alanine transferase) values. One DERAMAXX tablet-treated dog with a postoperative elevation in serum ALT, BUN, and total bilirubin values also vomited. None of the changes in clinical pathology values were considered clinically significant.

e. Statistical analysis: A Cochran-Mantel-Haenszel test statistic was calculated for the clinical evaluation variables of lameness at a walk, lameness at a trot, and pain on palpation. Modified ridit scores were used to represent the ordinal nature of the categories, and "site" was a stratification variable. A separate analysis was conducted to compare the test article and the placebo groups at each evaluation period.

   A generalized linear model assuming a binomial distribution and logit link function for the use (yes, no) of concomitant analgesic treatment was used. The concomitant analgesic treatment was defined as use within 24 hours post-surgery.

f. Conclusions: The results of this clinical study indicate that DERAMAXX™ Chewable Tablets, when administered orally at 3-4 mg/kg once daily for 7 days, are safe and effective for the control of orthopedic postoperative pain and inflammation. Statistically significant differences ($p<0.05$) at all postoperative evaluations for lameness, and pain on palpation demonstrate that DERAMAXX™ Chewable Tablets are effective for control of postoperative pain and inflammation in dogs following cranial cruciate surgery.

g. Adverse Reactions: Vomiting and diarrhea were the most common adverse events seen in both the DERAMAXX tablets- and placebo-treated groups.

Abnormal Health Findings in the Postoperative Orthopedic Pain Field Study*		
Clinical Observation	**DERAMAXX tablets N = 105**	**Placebo N = 102**
Vomiting	11	6
Diarrhea	6	7
Hematochezia	4	0
Melena	0	1
Anorexia	0	4
Incision site lesion (drainage, oozing)	11	6
Non-incision Skin Lesions (moist dermatitis, pyoderma)	2	0
Otitis Externa	2	0
Positive joint culture	1	0
Phlebitis	1	0
Hematuria	2	0
Conjunctivitis	1	2
Splenomegaly	1	0
Hepatomegaly	1	0
Death	0	1

*Dogs may have experienced more than one observation during the study. This table does not include one dog dosed at 16.92 mg/kg/day for the study duration. On the last day of treatment, this dog experienced vomiting, diarrhea, increased water intake and decreased appetite. Hematology and clinical chemistry values were unremarkable. The dog recovered uneventfully within 3 days of cessation of dosing.

2. Palatability Study

   a. Type of Study: Field Study

   b. Investigators:

Dr. Ben Jones Friendly Animal Clinic 2712 College Rd. Greensboro, NC 27408	Dr. Kristen Greeson Animal Clinic of Friendly Center 704-C Pembroke Rd. Greensboro, NC 27408
Dr. Janet Raczkowski Adams Farm Animal Hospital 5502 Adams Farm Lane Greensboro, NC 27407	Dr. Ronald Komich Greensboro Veterinary Hospital Inc. 3471 High Point Rd. Greensboro, NC 27406
Dr. Harvey Goho Total Care Veterinary Hospital 633 Greensboro Rd. High Point, NC 27260	

c. General Design: The study included one hundred (100) client-owned dogs. Dogs were dispensed two doses of DERAMAXX tablets and 1 dose of a palatable commercial vitamin product. Owners randomly dosed their dogs with one tablet daily on 3 consecutive days, and recorded their dogs' willingness to ingest the tablets from the hand, when placed in the food, or placed in the dog's mouth for 60 seconds.

d. Results: A total of 94% of dogs accepted the first dose of DERAMAXX tablets and 92% accepted the second dose.

e. Conclusions: DERAMAXX tablets are palatable to dogs.

III. Target Animal Safety

A. Two-Week Pharmacokinetics and Toxicity Study of Deracoxib in Dogs

1. Type of Study: Laboratory Study

2. Investigator: Randall P. Reed, BA
GD Searle & Co.
Skokie, Illinois

3. General design:

a. Purpose:

i) To determine the absorption of micronized deracoxib and the relationship of plasma concentrations of the test article with dosage and duration of dosing

ii) To assess the toxic effects of repeated dosing with the micronized test article

b. Test animals: Twelve Beagle dogs (male and female, 9-15 months of age, 8-14 kg body weight), were randomly assigned to four dosage groups (3 dogs/group).

c. Control: None

d. Dose form: Gelatin capsules filled with deracoxib

e. Route of administration: Orally to fasted dogs

f. Dosage: Table 2 lists the dose groups and duration of treatment

Table 2. Dose Groups for Deracoxib Tolerability Study

Group	Dosage (mg/kg/day)	No. Animals /Group	No. Days Treated
1	10	3	14
2	25	3	11
3	50	3	11
4	100	3	10

g. Test duration: Fourteen days

h. Parameters measured: general health, clinical observations, body weights, and necropsy, including gross and histopathology evaluations. Venous blood samples were collected at specified times post-dosing to measure plasma concentrations of deracoxib.

4. Results:

All dogs survived to the end of the study. Pharmacokinetic data collected in the study indicates that nonlinear elimination occurs with deracoxib at doses $\geq$ 10 mg/kg/day. Plasma levels of deracoxib may increase in a greater than dose proportional fashion at these doses.

There were no treatment related clinical observations in the 10 mg/kg group. Test article-related clinical observations at doses $\geq$ 25 mg/kg included vomiting and melena. In general, vomiting was observed sporadically in all animals in these dose groups. Melena was observed in most animals in the 25, 50, and 100 mg/kg treatment groups on Days 8 through 10. The incidence of melena in these groups appeared to be dose-related.

The body weights of dogs in the 25 and 50 mg/kg treatment groups were similar to pre-treatment values throughout the treatment period. By Day 8, one dog in the 50 mg/kg group and all three dogs in the 100 mg group exhibited slight weight losses that were likely associated with the administration of the test article.

Test-article related macroscopic findings in dogs given 10 mg/kg/day included moderate diffuse congestion of gut associated lymphoid tissues (GALT) in one dog and erosions/ulcers in the jejunum of another. Microscopic evaluation revealed erosions or ulcers in the jejunum and ileum of 2 dogs in the 10 mg/kg dose group.

Test-article related macroscopic findings at doses ≥ 25 mg/kg included small intestinal erosions/ulcers in one dog each from the 25 and 50 mg/kg treatment groups. At 100 mg/kg all dogs exhibited gastric ulcers and erosions/ulcerations of the small intestines. Evidence of intestinal hemorrhage in the dogs correlated with clinical observations of melena. There were no hepatic or renal lesions reported.

5. Conclusions:

Nonlinear elimination of deracoxib occurs at doses of 10 mg/kg and above. Elevated doses (≥25 mg/kg) are associated with COX-1 inhibition as evidenced by gastrointestinal signs.

The no effect dose level for micronized deracoxib administered once daily in gelatin capsules is less than 10 mg/kg. The frequency and severity of the gastrointestinal lesions increased with escalating doses. The gastrointestinal lesions reported in deracoxib-treated dogs at exaggerated doses are consistent with known non-steroidal anti-inflammatory drug (NSAID) induced adverse events.

B. 21-Day Safety Study in Dogs

1. Type of Study: Laboratory Study

2. Investigator: Ed Goldenthal PhD ATS
MPI Research Inc.
Mattawan, MI 49071-9399

3. General Design:

a. Purpose: To evaluate the safety of deracoxib in dogs

b. Test animals: Forty Beagle dogs (20 male and 20 female, 4-6 months of age, 6-9 kg body weight); four dogs per sex per treatment

c. Control: placebo tablets

d. Dose formulation: DERAMAXX tablets (final market tablet formulation)

e. Route of administration: Oral dosing within 30 minutes of feeding

f. Dosage used: 0, 4, 6, 8, 10 mg/kg body weight/day

g. Test duration: Twenty-one days

h. Parameters measured: clinical observations, food and water consumption, body weights, physical examinations, ophthalmic evaluations, hematology, clinical chemistry, urinalysis, buccal mucosal bleeding time, organ weights and anatomical pathology (macroscopic and microscopic)

4. Results:

All dogs survived to study termination. No adverse drug events were reported. There were no abnormal findings reported for clinical observations, food and water consumption, body weights, physical examinations, ophthalmic evaluations, organ weights, macroscopic pathologic examination, hematology, urinalysis or buccal mucosal bleeding time.

Clinical chemistry results showed a statistically significant ($p < 0.0009$) dose-dependent trend toward increased individual levels of blood urea nitrogen (BUN). Mean BUN values remained within the reference range at the labelled dose. No effects on other clinical chemistry values associated with renal function were reported. Renal histopathology revealed trace amounts of tubular degeneration/regeneration in all dose groups including placebo.

5. Conclusions:

DERAMAXX™ Chewable Tablets administered to healthy dogs within 30 minutes of feeding did not produce toxicity at doses ≤ 8 mg/kg once daily for 21 days. There was a dose-related increase in BUN values associated with administration of deracoxib tablets at all doses. No clear dose or test article relationship could be determined for the histopathologic changes noted.

C. 13-Week Capsule Study in Dogs with a 4-week Recovery Period

1. Type of Study: Laboratory (GLP) Study

2. Investigator: Dan W. Dalgard, DVM
Corning Hazelton, Inc.
Vienna, VA 22182

3. General Design:

a. Purpose:

i) To evaluate the subchronic toxicity of deracoxib when administered to dogs

ii) To evaluate the reversibility of any toxic effects following a 4-week recovery period

iii) To determine absorption of the test article and the relationship of plasma concentration with dosage and duration of dosing

b. Test animals: Forty-eight Beagle dogs (male and female, 4-6 months of age, 5-10 kg body weight) There were 4 dogs per sex per treatment group in the toxicity portion of the study. Additional animals were added to the control and high-dose groups for recovery groups (4 dogs/sex/dose). The pharmacokinetic section of the study used 3 dogs/sex/dose.

c. Control: Gelatin capsules

d. Dose formulation: Gelatin capsules filled with deracoxib

e. Route of administration: Oral

f. Dosage used: 0, 2, 4, and 8 mg/kg body weight/day

g. Test duration: Thirteen weeks

h. Parameters measured: clinical observations, food consumption, body weights, physical examinations, ophthalmoscopic and electrocardiograph evaluations, hematology, coagulation, clinical chemistry, urinalysis, organ weights and anatomical pathology (macroscopic and microscopic) Venous blood samples were

collected at specified times post-dosing to measure plasma concentrations of deracoxib.

4. Results:

All but one dog was in good health and survived to study termination. One high-dose (8 mg/kg) male dog died from bacterial septicemia associated with a renal abscess.

Analysis of plasma levels of deracoxib indicated that the drug was absorbed and systemically available at all doses throughout the study. Plasma concentrations increased with dose and were approximately proportional to dose over the dose range studied.

No test-article related changes were identified in clinical observations, physical examinations, or any of the other parameters measured.

5. Conclusions:

Deracoxib administered in capsules once daily for a period of 13 weeks, at doses up to 8 mg/kg body weight, did not produce toxicity in healthy dogs. The relationship between deracoxib administration and a renal abscess in one dog given 8 mg/kg is not clear.

IV. Human Safety

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "Not for use in humans. Keep this and all medication out of reach of children. Consult a physician in case of accidental ingestion by humans. For use in dogs only."

V. Agency Conclusions

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that DERAMAXX™ (deracoxib) Chewable Tablets for dogs, when used under labeled conditions of use are safe and effective for postoperative pain and inflammation associated with orthopedic surgery.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose and provide guidance in the control of orthopedic postoperative pain. Furthermore, the veterinarian monitors patients for possible adverse effects of the drug.

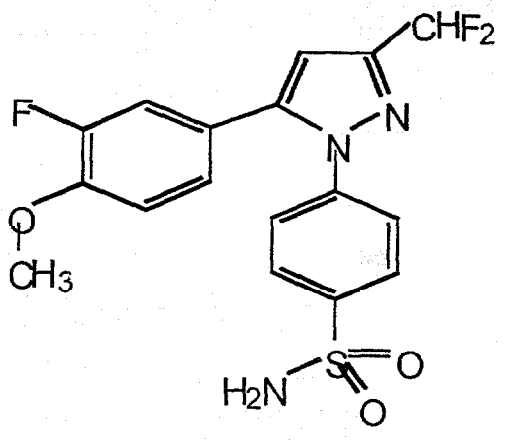
Deramaxx™ (deracoxib)

Chewable Tablets

For Oral Use In Dogs Only

Caution:
U.S. Federal Law restricts the use of this product by or on the order of a licensed veterinarian.

Description:
DERAMAXX (deracoxib) tablets are a non-narcotic, non-steroidal anti-inflammatory drug of the coxib class. DERAMAXX tablets are round, biconvex, chewable tablets that contain deracoxib formulated with beefy flavoring. The molecular weight of deracoxib is 397.38. The empirical formula is C17-H14-F3-N3-O3-S. Deracoxib is 4-[3-(Difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide, and can be termed a diaryl substituted pyrazole. The structural formula is:



Clinical Pharmacology

Mode of Action:
DERAMAXX tablets are a member of the coxib class of non-narcotic, non-steroidal, cyclooxygenase-inhibiting anti-inflammatory drugs for the control of postoperative pain and inflammation associated with orthopedic surgery.
Data indicate that deracoxib inhibits the production of PGE1 and 6-keto PGF1 by its inhibitory effects on prostaglandin biosynthesis[1]. Deracoxib inhibited COX-2 mediated PGE2 production in LPS-stimulated human whole blood[2].
Cyclooxygenase-1 (COX-1) is the enzyme responsible for facilitating constitutive physiological processes (e.g., platelet aggregation, gastric mucosal protection, renal perfusion).[3] Cyclooxygenase-2 (COX-2) is responsible for the synthesis of inflammatory mediators.[4] Both COX isoforms are constituitively expressed in the canine kidney.[5] At doses of 2-4 mg/kg/day, DERAMAXX tablets do not inhibit COX-1 based on *in vitro* studies using cloned canine cyclooxygenase[4]. The clinical relevance of this *in vitro* data has not been shown.
Although the plasma terminal elimination half-life for DERAMAXX tablets is approximately 3 hours, a longer duration of clinical effectiveness is observed.

Summary pharmacokinetics of DERAMAXX tablets are listed in Table 1.

Table 1: Pharmacokinetics of Deracoxib

Parameter	Value
Tmax [a]	2 hours
Oral Bioavailability (F) [a]	> 90% at 2 mg/kg
Terminal elimination half-life [b]	3 hours at 2-3 mg/kg 19 hours at 20 mg/kg
Systemic Clearance [b]	~ 5 ml/kg/min at 2 mg/kg ~1.7 ml/kg/min at 20 mg/kg
Volume of Distribution [c]	~ 1.5 L/kg
Protein binding [d]	> 90%

a Values obtained following a single 2.35 mg/kg dose
b Estimates following IV administration of deracoxib as an aqueous solution
c Based upon a dose of 2 mg/kg of deracoxib
d Based upon in vitro plasma concentrations of 0.1, 0.3, 1.0, 3.0, 10.0 µg/ml

Non-linear elimination kinetics are exhibited at doses above 8 mg/kg/day, at which competitive inhibition of constitutive COX-1 may occur.

Deracoxib is not excreted as parent drug in the urine. The major route of elimination of deracoxib is by hepatic biotransformation producing four major metabolites, two of which are characterized as products of oxidation and o-demethylation. The majority of deracoxib is excreted in feces as parent drug or metabolite.
Large intersubject variability was observed in drug metabolite profiles of urine and feces. No statistically significant differences between genders were observed.

Indications and Usage:
DERAMAXX Chewable Tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs ≥ 4 lbs (1.8 kg).

Dosage and Administration:
Always provide Client Information Sheet with prescription. The daily dose of DERAMAXX tablets for postoperative orthopedic pain is 3 to 4 mg/kg/day (1.4 – 1.8 mg/lb/day) as a single daily dose, as needed for 7 days. Since DERAMAXX tablet bioavailability is greatest when taken with food, postprandial administration is preferable. However, DERAMAXX tablets have been shown to be effective under both fed and fasted conditions; therefore, they may be administered in the fasted state if necessary. Administer DERAMAXX tablets prior to the procedure. Tablets are scored and dosage should be calculated in half-tablet increments. In clinical practice it is recommended to adjust the individual patient dose while continuing to monitor the dog's status until a minimum effective dose has been reached.

Contraindications:
Dogs with known hypersensitivity to deracoxib should not receive DERAMAXX tablets.

Warnings:
Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. **For use in dogs only.**

All dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to administration of any NSAID is recommended.

For technical assistance or to report suspected adverse events, call 1-800-332-2761

Precautions:
Plasma levels of deracoxib may increase in a greater than dose-proportional fashion above 8 mg/kg/day. DERAMAXX tablets have been safely used during field studies in conjunction with other common medications, including heartworm preventatives, anthelmintics, anesthetics, pre-anesthetic medications, and antibiotics. If additional pain medication is needed after a daily dose of DERAMAXX tablets, a non-NSAID class of analgesic may be necessary. It is not known whether dogs with a history of hypersensitivity to sulfonamide drugs will exhibit hypersensitivity to DERAMAXX tablets. The safe use of DERAMAXX tablets in dogs younger than 4 months of age, dogs used for breeding, or in pregnant or lactating dogs has not been evaluated.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. Appropriate monitoring procedures should be employed during all surgical procedures. NSAIDs may inhibit the prostaglandins, which maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. The use of parenteral fluids during surgery should be considered to decrease potential renal complications when using NSAIDs perioperatively. Since many NSAIDs possess the potential to produce gastrointestinal ulceration, concomitant use of DERAMAXX tablets with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored. The use of concomitantly protein-bound drugs with DERAMAXX tablets has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of DERAMAXX tablets has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

Animal Safety:
In a laboratory study, healthy young dogs were dosed with deracoxib tablets once daily, within 30 minutes of feeding, at doses of 0, 4, 6, 8, and 10 mg/kg body weight for 21 consecutive days. No adverse drug events were reported. There were no abnormal findings reported for clinical observations, food and water consumption, body weights, physical examinations, ophthalmic evaluations, organ weights, macroscopic pathologic evaluation, hematology, urinalyses, or buccal mucosal bleeding time. In the clinical chemistry results there was a statistically significant ($p<0.0009$) dose-dependent trend toward increased levels of blood urea nitrogen (BUN). Mean BUN values remained within historical normal limits at the label dose. No effects on other clinical chemistry values associated with renal function were reported. There was no evidence of renal, gastrointestinal, hepatic or biliary lesions noted during gross necropsy. Renal histopathology revealed trace amounts of tubular degeneration/regeneration in all dose groups including placebo, but no clear dose relationship could be determined. There was no histopathologic evidence of gastrointestinal, hepatic or biliary lesions.

In another study, micronized deracoxib in gelatin capsules was administered once daily to healthy young dogs at doses of 10, 25, 50, and 100 mg/kg body weight for periods up to 14 consecutive days. Food was withheld prior to dosing. Non-linear elimination kinetics occurred at all doses. At doses of 25, 50, and 100 mg/kg, reduced body weight, vomiting, and melena occurred. Necropsy revealed gross gastrointestinal lesions in dogs from all dose groups. The frequency and severity of the lesions increased with escalating doses. At 10 mg/kg, moderate diffuse congestion of gut associated lymphoid tissues (GALT) and erosions/ulcers in the jejunum occurred. At 100 mg/kg, all dogs exhibited gastric ulcers and erosions/ulcerations of the small intestines. There were no hepatic or renal lesions reported at any dose in this study.

In a 13-week study, deracoxib in gelatin capsules was administered to healthy dogs at doses of 0, 2, 4, and 8 mg/kg/day. No test-article related changes were identified in clinical observations, physical exams, or any of the other parameters measured. One dog in the 8 mg/kg dose group died from bacterial septicemia secondary to a renal abscess. The relationship between deracoxib administration and the renal abscess is not clear.

Palatability:
DERAMAXX tablets were evaluated for palatability in 100 client-owned dogs of a variety of breeds and sizes. Dogs received two doses of DERAMAXX tablets, one on each of two consecutive days. DERAMAXX tablets were accepted by 94% of dogs on the first day of dosing and by 92% of dogs on the second day of dosing.

Effectiveness:
DERAMAXX tablets were evaluated in a masked, placebo-controlled multi-site field study involving client -owned animals to determine effectiveness.

Field Study
In this study, 207 dogs admitted to veterinary hospitals for repair of a cranial cruciate injury were randomly administered DERAMAXX tablets or a placebo. Drug

administration started the evening before surgery and continued once daily for 6 days postoperatively. Effectiveness was evaluated in 119 dogs and safety was evaluated in 207 dogs. Statistically significant differences in favor of DERAMAXX tablets were found for lameness at walk and trot, and pain on palpation values at all post-surgical time points. The results of this field study demonstrate that DERAMAXX tablets, when administered daily for 7 days are effective for the control of postoperative pain and inflammation associated with orthopedic surgery.

Adverse Reactions:

A total of 207 dogs of forty three (43) different breeds, 1-15 years old, weighing 7-141 lbs were included in the field safety analysis. The following table shows the number of dogs displaying each clinical observation.

Abnormal Health Findings in The Postoperative Orthopedic Pain Field Study*		
Clinical Observation	**DERAMAXX tablets N = 105**	**Placebo N= 102**
Vomiting	11	6
Diarrhea	6	7
Hematochezia	4	0
Melena	0	1
Anorexia	0	4
Incision site lesion (drainage, oozing)	11	6
Non-incision Skin Lesions (moist dermatitis, pyoderma)	2	0
Otitis Externa	2	0
Positive joint culture	1	0
Phlebitis	1	0
Hematuria	2	0
Conjunctivitis	1	2
Splenomegaly	1	0
Hepatomegaly	1	0
Death	0	1

*Dogs may have experienced more than one of the observations during the study.

**This table does not include one dog that was dosed at 16.92 mg/kg/day for the study duration. Beginning on the last day of treatment, this dog experienced vomiting, diarrhea, increased water intake and decreased appetite. Hematology and clinical chemistry values were unremarkable. The dog recovered uneventfully within 3 days of cessation of dosing.

Incisional drainage was most prevalent in dogs enrolled at a single study site. There were no statistically significant changes in the mean values for hepatic or renal clinical pathology indices between DERAMAXX tablet- and placebo-treated dogs. Four DERAMAXX tablet-treated dogs and two placebo-treated dogs exhibited elevated bilirubin during the dosing phase. One DERAMAXX tablet-treated dog exhibited elevated ALT, BUN and total bilirubin and a single vomiting event. None of the changes in clinical pathology values were considered clinically significant.

The results of this field study demonstrate that DERAMAXX tablets, when administered daily for 7 days to control postoperative orthopedic pain and inflammation in dogs, are well tolerated.

Storage Conditions:

DERAMAXX tablets should be stored at room temperature between 59° and 86°F (15-30°C).

Keep this and all medications out of reach of children.

How Supplied:

DERAMAXX tablets are available as 25 mg and 100 mg round, brownish, half-scored tablets in 7, 30 and 90 count bottles.

Manufactured by: G.D.Searle & Co.
Caguas, Puerto Rico

Manufactured for: Novartis Animal Health US, Inc.
Greensboro, NC 27408 USA

References:

1. Data on File
2. Data on File
3. Smith, et al.: "Pharmacological Analysis of Cyclo-oxygenase –1 in Inflammation," Proc. Natl. Acad. Sci. USA (October 1998) 95: 13313-13318, Pharmacology.
4. Zhang, et al.: "Inhibition of Cyclo-oxygenase-2 Rapidly Reverses Inflammatory Hyperalgesia and Prostaglandin E2 Production," *JPET*, (1997) 283: 1069-1075.
5. Verburg, KM et al. "Cox-2 Specific Inhibitors: Definition of a New Therapeutic Concept." Amer J of Therapeutics 8, 49-64, 2001.
6. Data on File

NADA # 141-203, Approved by FDA

NAH/DXB-T/VI/Draft

6/02

Deramaxx™
(deracoxib)

DERAMAXX ™ Chewable Tablets: Information for Dog Owners

DERAMAXX Chewable Tablets are for the control of pain and inflammation following orthopedic surgery in dogs.

This summary contains important information about DERAMAXX tablets. You should read this information before you start giving your dog DERAMAXX tablets. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or you want to know more about DERAMAXX tablets.

What is DERAMAXX?

DERAMAXX tablets are a prescription non-steroidal anti-inflammatory drug (NSAID) of the coxib class. They are indicated for the control of postoperative pain and inflammation associated with orthopedic (bone) surgery in dogs. The tablets are flavored to make administration more convenient.

What kind of results can I expect when my dog takes DERAMAXX tablets for postoperative orthopedic pain and inflammation?

DERAMAXX tablets allow your dog to recover more comfortably by controlling pain and inflammation that follow orthopedic surgery.

- Control of pain and inflammation may vary from dog to dog.
- If DERAMAXX tablets are not given according to your veterinarian's directions, your dog's pain may return.
- Consult your veterinarian if your dog appears to be uncomfortable.

What dogs should not take DERAMAXX tablets?

Your dog should not be given DERAMAXX tablets if s/he:

- Has had an allergic reaction to deracoxib, the active ingredient in DERAMAXX tablets
- Has had an allergic reaction (such as hives, facial swelling, or red or itchy skin) to aspirin or other NSAIDs
- Is presently taking aspirin, other NSAIDs, or corticosteroids (unless directed by your veterinarian).

DERAMAXX tablets should only be given to dogs.

People should not take DERAMAXX tablets. Keep DERAMAXX tablets and all medication out of reach of children. Call your physician immediately if you accidentally take DERAMAXX tablets.

What to discuss with your veterinarian before giving DERAMAXX tablets?

Tell your veterinarian about:

- Any side effects your dog has experienced from DERAMAXX tablets or other NSAIDs
- Any digestive upset (vomiting or diarrhea) your dog has had
- Any kidney disease your dog has had
- Any other medical problems or allergies that your dog has now or has had in the past
- All medications that you are giving your dog or plan to give your dog, including those you can get without prescription and any dietary supplements
- If you plan to breed your dog, or if your dog is pregnant or nursing

Talk to your veterinarian about:

- The orthopedic surgery your dog will undergo
- What tests might be done before surgery is performed or DERAMAXX tablets are prescribed
- The signs of pain or inflammation that may occur after surgery
- Normal events that can be expected after your dog undergoes surgery

- The proper amount of exercise after surgery to aid recovery
- How often your dog may need to be examined by your veterinarian
- The risks and benefits of using DERAMAXX tablets

How to give DERAMAXX tablets to your dog.

DERAMAXX tablets should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of DERAMAXX tablets is right for your dog and for how long they should be given (no longer than 7 days). Do not change the way you give DERAMAXX tablets to your dog without first speaking with your veterinarian. DERAMAXX tablets should be given by mouth and may be given with or without food.

What are the possible side effects that may occur in my dog during therapy with DERAMAXX tablets?

DERAMAXX tablets, like all other drugs, may cause some side effects in individual dogs. Serious but rare side effects have been reported in dogs taking non-steroidal anti-inflammatory drugs (NSAIDs). It is important to stop the medication and contact your veterinarian immediately if you think your dog may have a medical problem or side effect while on DERAMAXX tablets. If you have additional questions about possible side effects, talk with your veterinarian or call 1-800-332-2761.

Look for the following side effects that may indicate that your dog is having a problem with DERAMAXX tablets or may have another medical problem:

- Vomiting
- Change in bowel movements such as diarrhea or change in stool color
- Change in drinking or urination
- Decrease in appetite

Can DERAMAXX tablets be given with other medications?

DERAMAXX tablets should not be given with other non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids (for example, aspirin, carprofen, etodolac, prednisone), unless directed by your veterinarian.

Tell your veterinarian about all medications that you have given your dog in the past, and any medications that you are planning to give with DERAMAXX tablets. This should include any medications that you can get without a prescription and any dietary supplements. Your veterinarian may want to evaluate the potential for any drug interactions and to assure drug compatability.

What can I do in case my dog eats more than the prescribed amount of DERAMAXX tablets?

Contact your veterinarian immediately if your dog eats more than the prescribed amount of DERAMAXX tablets.

What else should I know about DERAMAXX tablets?

This sheet provides a summary of information about DERAMAXX tablets. If you have any questions or concerns about DERAMAXX tablets or postoperative orthopedic pain and inflammation, talk to your veterinarian.

As with all prescribed medications, DERAMAXX tablets should only be given to the dog for which they are prescribed. They should be given to your dog only for the condition for which they were prescribed, at the prescribed dose, for orthopedic postoperative pain and inflammation, and for no longer than 7 days.

NADA 141-203
Approved by FDA

NAH/DXB-T/CI/Draft 5/02

P06004-1

Dosage & Administration. For complete product information, see package insert. NAH/DXB-T/7ct/25/BL/1

Deramaxx™ (deracoxib)

7 chewable tablets

A coxib-class NSAID
For Use in Dogs Only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA#141-203, Approved by FDA
Manufactured for Novartis Animal Health US, Inc. Greensboro, NC 27408

NOVARTIS

25 mg

Storage Conditions: Store at room temperature between 59° and 86°F (15-30°C). **WARNINGS: Keep this and all medications out of the reach of children.**

UPC @ 100%
Minimum height 3/8"
3 XXXX-XXXX-XX

BAR CODE FPO

P06005-1

Dosage & Administration. For complete product information, see package insert. NAH/DXB-T/7ct/100/BL/1

Deramaxx™ (deracoxib)

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NADA#141-203, Approved by FDA
Manufactured for Novartis Animal Health US, Inc. Greensboro, NC 27408

NOVARTIS

100 mg

Storage Conditions: Store at room temperature between 59° and 86°F (15-30°C). **WARNINGS: Keep this and all medications out of the reach of children.**

UPC @ 100%
Minimum height 3/8"
3 XXXX-XXXX-XX

BAR CODE FPO